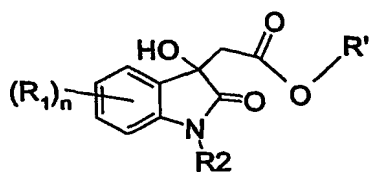


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Claims:

1. A method for the manufacture of pharmaceuticals or of a compound of the formula I or II defined below, comprising a method for the manufacture of esters of the formula I,



(I)

wherein n is a number from 0 to 4,

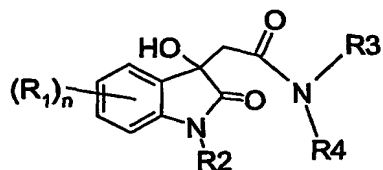
each R_1 is, independently of the other substituents R_1 , unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, alkylsulfonyl, sulfonyl alkyl, N-mono- or N,N-disubstituted or unsubstituted aminosulfonyl alkyl, hydroxy, mercapto, nitro, halogen, cyano, carboxamido, N-mono- or N,N-disubstituted carboxamido, carboxhydrazido, unsubstituted or substituted alkoxy carbonyl, unsubstituted or substituted alkoxy, formyl or other alkanoyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, alkanoyloxy, N-mono- or N,N-disubstituted or unsubstituted amino, unsubstituted or substituted hydrazino, or is a residue of a boronic acid or an ester thereof;

R_2 is hydrogen or unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy carbonyl, unsubstituted or substituted arylsulfonyl, unsubstituted or substituted alkylsulfonyl, unsubstituted or substituted aryl, carbamoyl or N-mono- or N,N-disubstituted carbamoyl, silyl substituted by three moieties independently selected from unsubstituted or substituted alkyl and substituted or unsubstituted aryl, or acyl, and

R' is unsubstituted or substituted alkyl,

or of amides of the formula II,

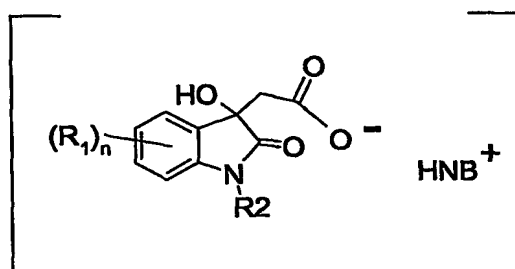
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(II)

wherein n , R_1 and R_2 are as defined under formula I and R_3 and R_4 are, independently of each other, unsubstituted or substituted alkyl or together form an unsubstituted or substituted alkylene bridge (thus forming a ring with the binding nitrogen) or an alkylene bridge to which a phenyl or a C_3 - C_8 -cycloalkyl ring is condensed at two vicinal carbon atoms of the alkylene bridge

where a starting material of the formula III,

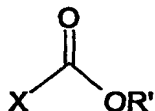


(III)

wherein n , R_1 and R_2 have the meanings given under formula I and NB is a tertiary nitrogen base where the nitrogen is not part of a ring,

is reacted

(a) for the synthesis of an ester of the formula I with an active carbonic ester of the formula IV,

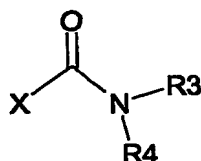


(IV)

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wherein X is halogen and R' is as defined under formula I, to give the corresponding ester of the formula I, or

(b) for the synthesis of an amide of the formula II with an active amido carbonic acid derivative of the formula V,



(V)

wherein X is halogen and R3 and R4 are as defined under formula II, to give the corresponding compound of the formula II.

2. The method according to claim 1 for the synthesis of a substituted amide of the formula II as defined in claim 1 and variant (b), preferably wherein R₁ is nitro, cyano or halogen or a residue of a boronic acid or an ester thereof and n is 1 or 2.

3. The method according to claim 1 where the substituents and symbols, as far as present in the compounds of the formulae I to V, have the following meanings:

n is an integer from 0 to 3;

each R₁ is, independently, lower alkyl; lower alkyl substituted by up to three moieties selected from N,N-di-lower alkylamino, N-phenyl-lower alkylamino, N,N-bis (phenyl-lower alkyl)-amino, N,N-di-lower acylamino, N-lower acylamino, alkylated and/or acylated hydrazino of the formula R₂₀R₂₁N-N(R₂₂)- wherein R₂₀ is alkyl or acyl or substituted alkyl and R₂₁ is hydrogen or R₂₀ and R₂₂ is hydrogen or acyl; halo-lower alkyl; C₃-C₁₀-cycloalkyl; lower alkoxy; aryl-lower alkoxy; lower alkanoyloxy; N,N-di-lower alkylamino; N-phenyl-lower alkylamino, N,N-bis (phenyl-lower alkyl)-amino, N'-phenyl-lower alkylhydrazino, N',N'-bis (phenyl-lower alkyl)-hydrazino, each of which contains phenyl unsubstituted or substituted; N',N'-di-lower alkylhydrazino; unsubstituted or substituted aryl; unsubstituted or substituted heterocyclyl; unsubstituted or lower alkyl substituted and/or mono- or di-oxosubstituted heterocyclenyl or heterocyclyl; alkylsulfonyl; sulfonyl alkyl; unsubstituted, N-mono- or N,N-disubstituted aminosulfonyl alkyl; hydroxy; mercapto; nitro; halogen; cyano; carboxamido or carboxhydrazido;

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N-mono- or N,N-disubstituted carboxamido; unsubstituted or substituted alkoxy carbonyl; unsubstituted or substituted alkoxy; formyl or other alkanoyl; unsubstituted or substituted alkenyl; unsubstituted or substituted alkynyl; or R₁ is a residue of a boronic acid or an ester thereof;

R₂ is hydrogen or unsubstituted or substituted alkyl with substituents as defined for substituted lower alkyl R₁; unsubstituted or substituted lower alkoxy carbonyl wherein the substituents are independently selected from lower alkyl and phenyl-lower alkyl; unsubstituted or substituted arylsulfonyl, unsubstituted or substituted alkylsulfonyl; unsubstituted or substituted phenyl; carbamoyl or N-mono- or N,N-disubstituted carbamoyl; silyl substituted by three moieties independently selected from unsubstituted or substituted lower alkyl as defined for unsubstituted or substituted lower alkyl R₁ and from substituted or unsubstituted aryl as defined above for R₁; or acyl selected from lower alkoxy carbonyl, unsubstituted or substituted aryloxy carbonyl or unsubstituted or substituted aryl-lower alkoxy carbonyl, each with unsubstituted or substituted aryl as defined above for R₁, or aryl-carbonyl, aryl-lower alkyl carbonyl or (unsubstituted or substituted lower alkyl)-carbonyl, and

R' is unsubstituted or substituted alkyl;

and in formula II R₃ and R₄ is lower alkyl or R₃ and R₄ together form a lower alkylene bridge.

4. The method according to any one of claims 1 to 3, wherein NB is a tri-lower alkylamine, especially triethylamine.

5. A compound of the formula I as defined in claim 1, or a salt thereof, wherein n is 1 - 4, and

each R₁ is unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, sulfonyl alkyl, N-mono- or N,N-disubstituted or unsubstituted aminosulfonyl alkyl, hydroxy, mercapto, nitro, halogen, cyano, carboxamido, N-mono- or N,N-disubstituted carboxamido, carboxhydrazido, unsubstituted or substituted alkoxy carbonyl, unsubstituted or substituted alkoxy, formyl or other alkanoyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted

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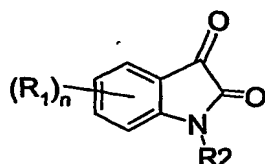
cycloalkyl, alkanoyloxy, N-mono- or N,N-disubstituted or unsubstituted amino, unsubstituted or substituted hydrazino, or is a residue of a boronic acid or an ester thereof;

provided that when n is 1 and R₁ is lower alkyl, R₁ is located in the position para to the isatine nitrogen (5-position),

, and with the exception of a compound of the formula I wherein R₁ is 5- or 7-chloro or 5- or 7- hydroxy or alkoxy or alkanoyloxy, and with further exception of the compound 3-hydroxy-3-butyloxycarbonylmethyl-7-ethyl-6-hydroxy-indolidin-2-one.

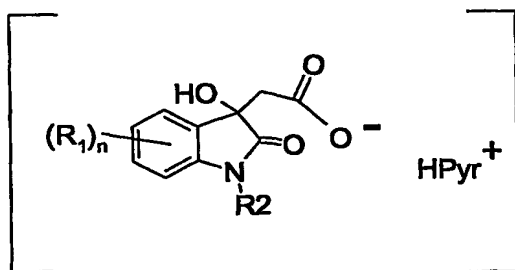
6. A compound of the formula II as defined in any one of claims 1 or 3, or a salt thereof.

7. A method according to any one of claims 1 to 4 wherein the compound of the formula III is obtained by reaction of an isatine derivative of the formula VI,



(VI)

wherein n, R₁ and R₂ have the meanings given under formula I in any one of claims 1 or 3, with malonic acid in the presence of a pyridine, followed by conversion of the resulting product of the formula III*,



(III*)

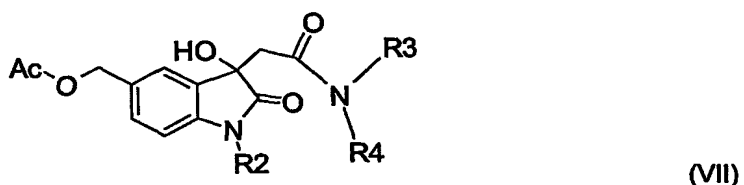
wherein n, R₁ and R₂ have the meanings given under formula I and HPyr⁺ is the respective cation resulting from a pyridine as mentioned above, into the salt of the base NB given in formula III.

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8. A method according to claim 7, where the reaction of the compound of the formula VI with malonic acid in the presence of a pyridine and optionally a co-solvent, the subsequent conversion into the salt of the formula III with the base NB and reaction a) or b) of claim 1 take place in the same reaction vessel.

9. A compound of the formula III* as mentioned in claim 7, wherein n, R1 and R2 have the meanings given for compounds of the formula I or II in claim 1 or 3, except for a compound of formula I wherein n is zero or 1 and R1 is lower alkyl.

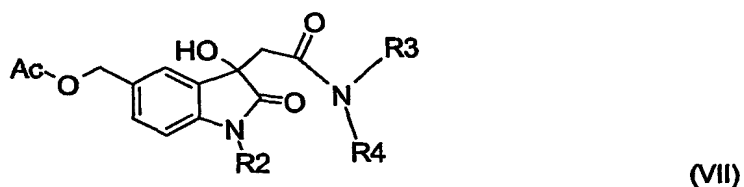
10. The method according to any one of claims 1 to 4 and 7 or 8, where in a further step an amide of the formula II wherein n is zero and thus R₁ is absent is converted to a compound of the formula VII,



wherein Ac is acetyl and R2, R3 and R4 have the meanings indicated for compounds of the formula II with the proviso that in the compound of the formula II and of the formula VII, R2 is other than hydrogen;

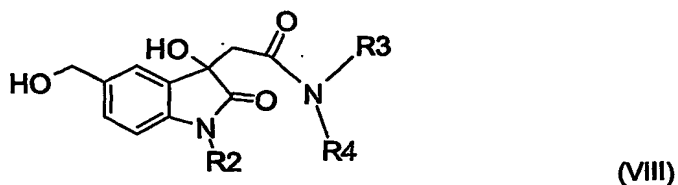
by the reaction with formaldehyde or a precursor thereof in the presence of acetic acid.

11. A method according to claim 10, further comprising transforming the compound of the formula VII



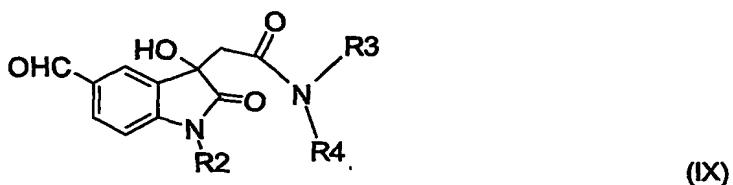
into the corresponding free alcohol of the formula VIII,

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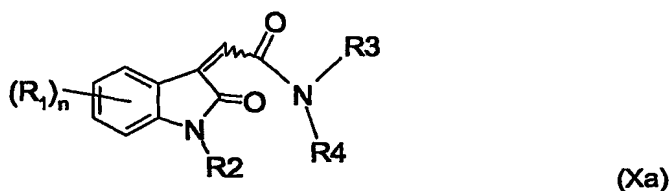
wherein R2, R3 and R4 are as defined under formula VII.

12. A method according to claim 11, further comprising reacting the alcohol of the formula VIII shown in claim 11 with an oxidising agent to give the corresponding compound of the formula IX



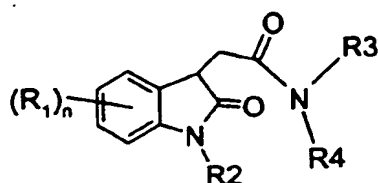
wherein R2, R3 and R4 have the meanings given under formula VII.

13. A method according to any one of claims 1 to 4, where an amide compound of the formula II wherein R2 has one of the meanings given in claims 1 or 3 other than hydrogen is further reacted with a dehydrating agent to give a compound of the formula Xa,



wherein n and R₁ are as defined under formula I and R3 and R4 are, independently of each other, unsubstituted or substituted alkyl, or together form an unsubstituted or substituted alkylene bridge.

14. A method according to claim 13, further comprising reducing the compound of the formula Xa in the presence of a reductant to a compound of the formula Xb,

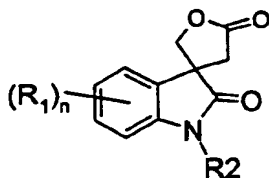


(Xb)

wherein n , R_1 , R_2 , R_3 and R_4 are as defined for a compound of the formula Xa in claim 13.

15. A method according to any one of claims 1 to 4, where a compound of the formula Xb as defined in claim 14 is obtained by hydrogenation of the benzylic 3-hydroxy group in a compound of the formula II.

16. A method for the synthesis of a tryptamine derivative having pharmacologically useful properties, or a method for preparing a spiro indole of the formula XI,



(XI)

comprising converting a compound of the formula Xb as defined in claim 14 to a spiro indole of the formula XI by reaction with formaldehyde or a precursor thereof, wherein n , R_1 and R_2 are as defined in claim 14.

17. A compound of the formulae VII or VIII as defined in claim 11 or of the formula IX as defined in claim 12 or of the formula Xa as defined in claim 13 or of the formula Xb as defined in claim 14 or of the formula XI as defined in claim 16.

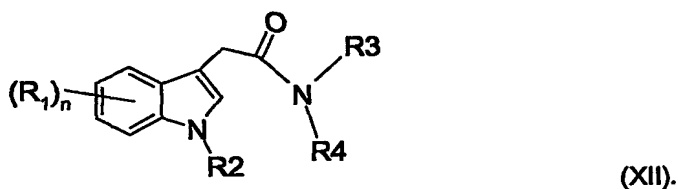
18. A method according to any one of claims 1 to 3, further comprising reducing a compound of the formula II wherein n , R_2 , R_3 and R_4 are, independently of each other, as defined in claim 1, and R_1 is unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycdyl, alkylsulfonyl, sulfonyl alkyl, N-mono- or N,N-disubstituted or unsubstituted aminosulfonyl alkyl, hydroxy, mercapto, nitro, halogen, cyano, carboxamido, N-mono- or N,N-disubstituted carboxamido, unsubstituted or substituted alkoxy, unsubstituted or substituted alkoxy, formyl or other alkanoyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted

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cycloalkyl, alkanoyloxy, N -mono- or N,N-disubstituted or unsubstituted amino, or is a residue of a boronic acid or an ester thereof,

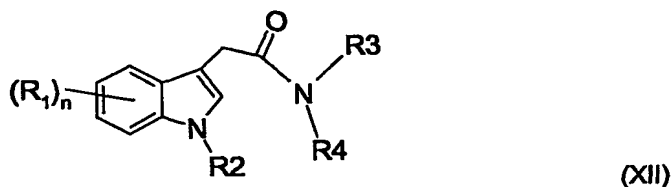
in the presence of a complex hydride.

19. The method according to claim 18 wherein as reductant a borane di-lower alkyl sulfide is used, resulting in the formation of the corresponding indole of the formula XII



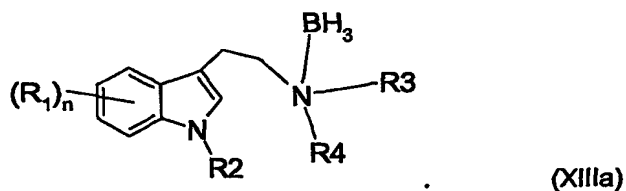
wherein the symbols and moieties are as defined in claim 18.

20. A compound of the formula XII

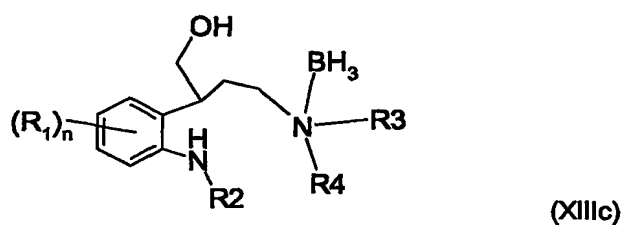
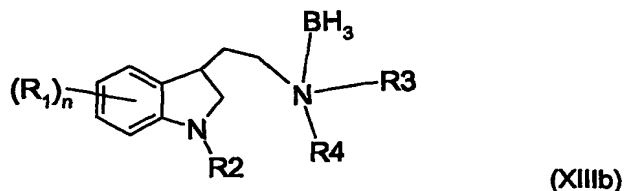


wherein n, R₁, R₂, R₃ and R₄ are as defined for formula II in claim 18, provided that R₁ is not 5-methoxy if n is 1.

21. The method according to claim 18 where reaction of the compound of the formula II takes place in the presence of an alkali metal borohydride and a boron trifluoride etherate, yielding a mixture containing compounds of the formulae XIIIa, XIIIb and XIIIc,

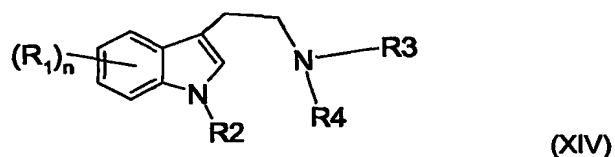


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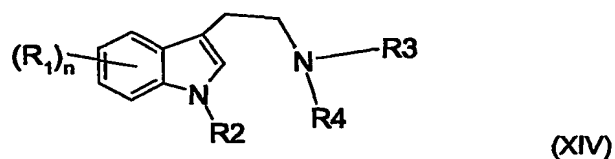
wherein n , R_1 , R_2 , R_3 and R_4 are as defined for the starting compounds of the formula II.

22. A process according to claim 21, further comprising the conversion of the mixture of compounds XIIIa, XIIIb and XIIIc into a compound of the formula XIV



wherein n , R_1 , R_2 , R_3 and R_4 are as defined under formula XIIIa, XIIIb and XIIIc in claim 21, by reaction with diazabicyclo[2.2.2]octane and subsequent dehydrogenation or oxidation with an oxidant.

23. A compound of the formula XIV

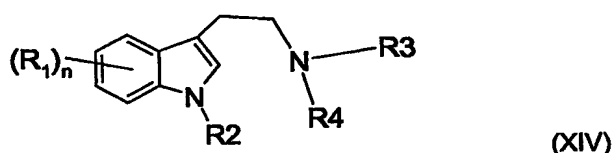


wherein n , R_2 , R_3 and R_4 are as defined in claim 1 and R_1 is a residue of a boronic acid or ester thereof, lower alkyl, lower alkyl substituted by up to three moieties selected from N,N-di-lower acylamino and N-lower acylamino, C_3 - C_{10} -cycloalkyl, C_2 - C_4 alkoxy, nitro, halogen, lower alkanoyloxy, unsubstituted or substituted aryl, unsubstituted or lower alkyl substituted

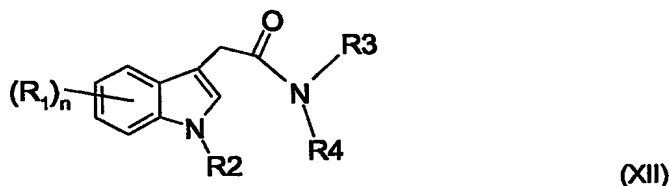
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and/or mono- or di-oxosubstituted nitrogen-heterocyclenyl or nitrogen-heterocyclyl, sulfonyl alkyl, mercapto, C₂-C₈alkanoyl, unsubstituted or substituted alkenyl, or unsubstituted or substituted alkynyl, or a salt thereof.

24. Conversion of a compound of the formula XIV according to claim 22



or of the formula XII according to claim 19,



where n, R₁, R₃ and R₄ are as defined in claim 22 and R₂ is hydrogen, respectively,

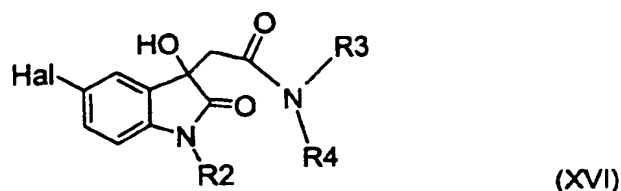
by introduction of a moiety R₂ which is unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy carbonyl, unsubstituted or substituted aryl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, silyl substituted by three moieties independently selected from unsubstituted or substituted alkyl and substituted or unsubstituted aryl, or acyl; wherein unsubstituted or substituted alkyl is introduced by reaction with a strong base, e.g. NaH, with a corresponding unsubstituted or substituted alkyl derivative of the formula XV,



wherein Alk is unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy carbonyl, unsubstituted or substituted aryl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, and L is a leaving group, to give the corresponding compound of the formula XII or XIV wherein R₂ is unsubstituted or substituted alkyl; or acyl is introduced by reaction with the corresponding acylhalogenides or mixed or symmetric acid anhydrides with one or two

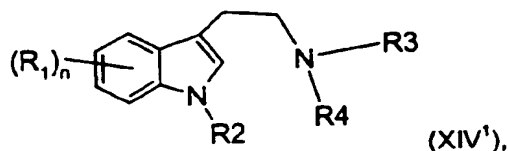
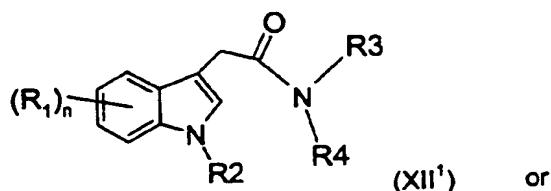
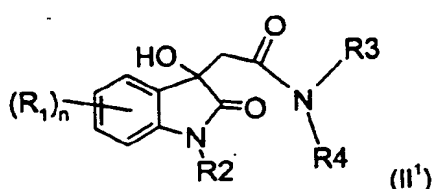
of the corresponding acyl moieties; or the silyl derivatives are introduced using the corresponding silylhalogenides, respectively; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said conversion.

25. A process for the introduction into a compound of the formula II as defined in claim 18 where n is zero and the other substituents are as defined in claim 1 or 3, of a moiety R₁ resulting from electrophilic substitution reaction with a halogen R₁ by reaction with a halo-succinimide, or nitro by reaction with nitric acid, leading to a compound of the formula XVI,



wherein Hal is nitro or halogen, and R₂, R₃ and R₄ have the meanings given for a compound of the formula II; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

26. A process for the manufacture of a compound of the formula II', XII' or XIV', respectively,



wherein n is 1 or 2, R₁ is unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl and R₂, R₃ and R₄ have the meanings given under formula II in claim 1 or 3, comprising reacting a compound of the formula II as defined in claim 18 for the synthesis of compound II', or of the formula XII as defined in any one of claims 19, 20 or 24 for the synthesis of compound XII', or of the formula XIV as defined in any one of claims 22, 23 or

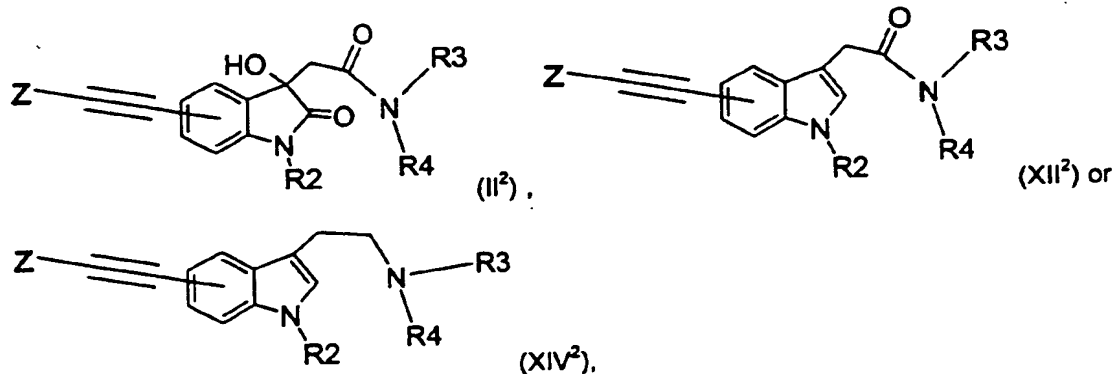
24 for the synthesis of compound XIV¹, wherein in each case n is 1 or 2 and R¹ is halogen, under the conditions of the Suzuki coupling or analogous conditions with a compound of the formula (A),



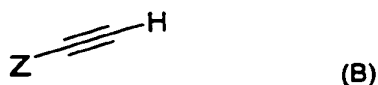
(A)

wherein Ar is unsubstituted or substituted aryl or heterocyclyl and Y is OH, into the corresponding compounds of the formulae II¹, XII¹ or XIV¹, respectively; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

27. A process for the reaction of a compound of the formula II as defined in claim 18, of the formula XII as defined in any one of claims 19, 20 or 24, or of a compound of the formula XIV as defined in any one of claims 22, 23 or 24, with the proviso that in each of the compounds of the formulae II, XII and XIV, n is 1 and R¹ is halogen, to a compound of the formulae II² from compound II, to a compound of the formula XII² from compound XII or to a compound of the formula XIV² from compound XIV, respectively,



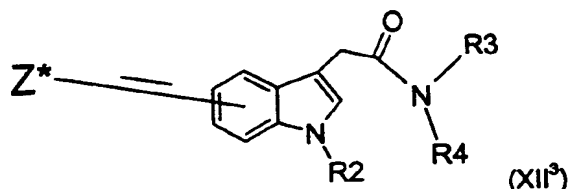
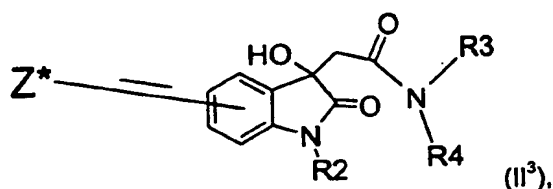
wherein Z is unsubstituted or substituted alkyl, and R², R³ and R⁴ are as defined under formula II, respectively, by coupling under the conditions of or analogous to a Sonogashira coupling with a compound of the formula (B),



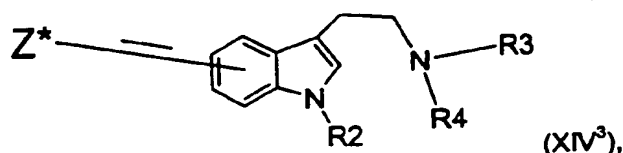
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wherein Z is unsubstituted or substituted alkyl, to yield the corresponding compounds of the formulae II², XII² or XIV², respectively; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

28. A process for the reaction of compounds of the formula II as defined in claim 22, of the formula XII as defined in any one of claims 19, 20 or 24, or of compounds of the formula XIV as defined in any one of claims 22, 23 or 24, with the proviso that in each of the compounds of the formulae II, XII and XIV n is 1 and R1 is halogen, to compounds of the formulae II³ (from compound II), XII³ (from compound XII) or XIV³ (from compound XIV) respectively,

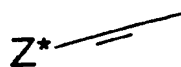


or



wherein Z* is unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted arylsulfonyl, unsubstituted or substituted alkylsulfonyl, (Y)₂N-sulfonyl wherein each Y, independently of the other, is hydrogen or unsubstituted or substituted alkyl; or Z* is alkoxy carbonyl, cyano or unsubstituted or substituted heterocyclyl, and R2, R3 and R4 are as defined for compounds of the formula II,

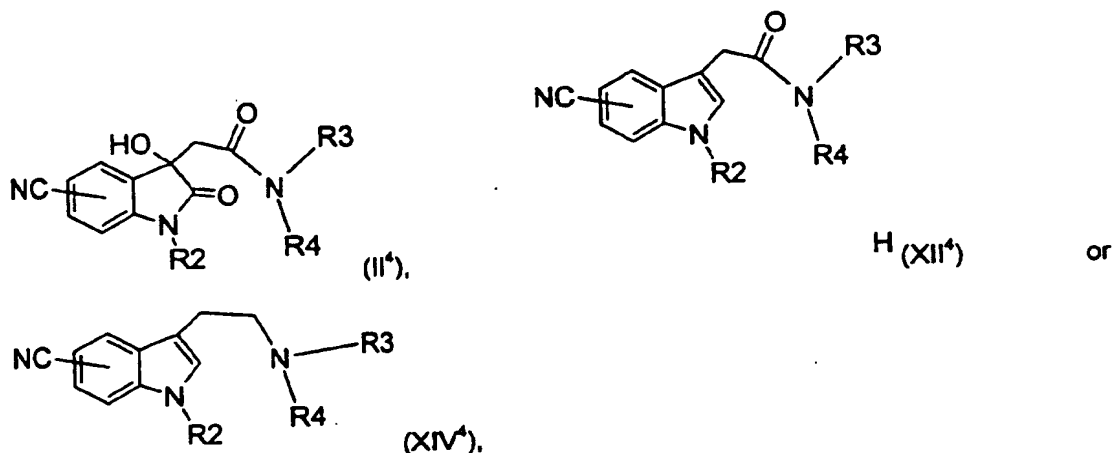
by coupling with a compound of the formula (C),



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wherein Z* is as just defined under conditions of or analogous to the Heck reaction to yield the corresponding compounds of the formulae II³, XII³ or XIV³, respectively; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

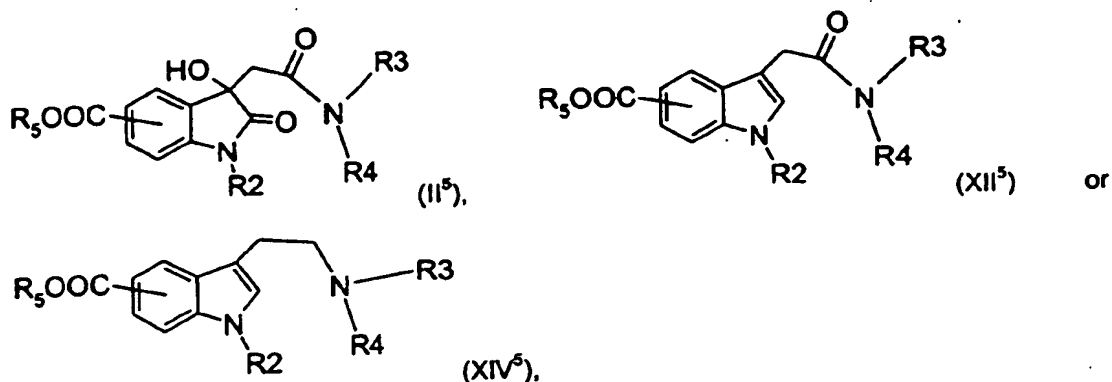
29. A process for the reaction of compounds of the formula II as defined in claim 22, of the formula XII as defined in any one of claims 19, 20 or 24, or of compounds of the formula XIV as defined in any one of claims 22, 23 or 24, with the proviso that in each of the compounds of the formulae II, XII and XIV n is 1 and R1 is halogen, to compounds of the formulae II⁴ (from compound II), XII⁴ (from compound XII) or XIV⁴ (from compound XIV) respectively.



wherein R2, R3 and R4 are as defined above for a compound of the formula II, by reaction with a cyanide salt in the presence of a palladium catalyst; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process..

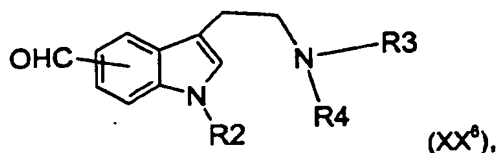
30. A process for the reaction of compounds of the formula II as defined in claim 22, of the formula XII as defined in any one of claims 19, 20 or 24, or of compounds of the formula XIV as defined in any one of claims 22, 23 or 24, with the proviso that in each of the compounds of the formulae II, XII and XIV n is 1 and R1 is halogen to compounds of the formulae II⁵ (from compound II), XII⁵ (from compound XII) or XIV⁵ (from compound XIV) respectively,

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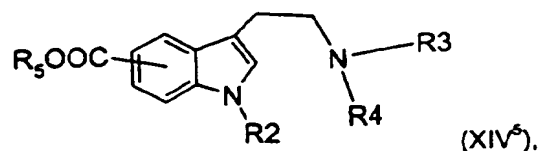
wherein R₅ is unsubstituted or substituted alkyl, or unsubstituted or substituted aryl, and R₂, R₃ and R₄ are as defined for the compounds of the formula II, by reaction with CO in the presence of the corresponding alcohol R₅-OH; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

31. A process for the reaction of a compound of the formula XIV as defined in any one of claims 22, 23 or 24 where n is 1 and R₁ is halogen, comprising converting it into the corresponding compound of the formula XX⁶,

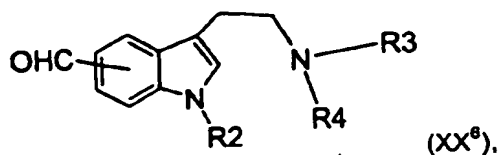


wherein R₂, R₃ and R₄ are as defined for the compound of the formula XIV, by reaction with first a lithium alkyl compound to form the lithio derivative and then with DMF or triethyl formate, to obtain the compound of the formula XX⁶ after hydrolysis; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

32. A compound of the formula XIV⁵

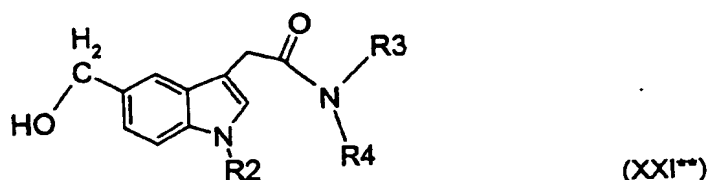


or of the formula XX⁶



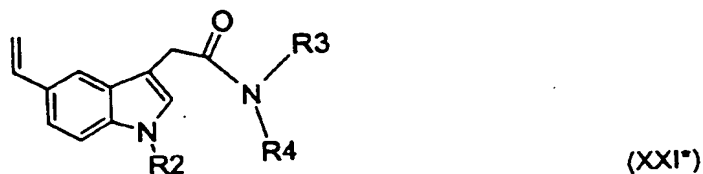
wherein R₂, R₃, R₄ and R₅ are as defined in claim 1 for formula II, provided that one of R₃ or R₄ is not methyl and R₃ and R₄ together are not phthalyl, or a salt thereof.

33. A process for the manufacture of a compound of the formula XXI^{**}



wherein R₂, R₃ and R₄ have the meanings indicated for compounds of the formula XX⁶ in claim 31, by reduction of the compound of the formula XX⁶ in the presence of a selective transition metal catalyst; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

34. A process for the manufacture of a compound of the formula XXI^{*},



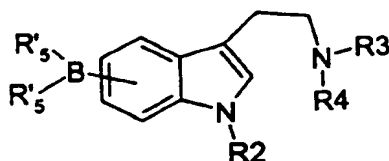
wherein R₂, R₃ and R₄ have the meanings indicated for compounds of the formula XX⁶ in claim 31,

by conversion of a compound of the formula XX⁶ as defined in claim 31 into the corresponding compound of the formula XXI^{*} by reaction with a Wittig or Wittig Horner

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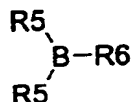
reagent in the presence of a suitable base; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

35. A process for the reaction of a compound of the formula XIV as defined in any one of claims 22, 23 or 24 where n is 1 and R_1 is halogen, comprising converting it into the corresponding compound of the formulae XX^7 ,

(XX⁷)

wherein R_2 , R_3 and R_4 are as defined for the compound of the formula XIV, and each of R'_5 independently is hydroxy or an alkoxy residue of a lower alcohol, or the 2 residues R'_5 together are C_2-C_8 alkylene-dioxy,

by reaction with first a lithium alkyl compound to form the lithio derivative, and then with an ester of boric acid B,



(B)

wherein each of R_5 and R_6 independently is an alkoxy residue of a lower alcohol, or the 2 residues R_5 together are C_2-C_8 alkylene-dioxy,

and subsequent hydrolysis, to obtain the compound of the formula XX^7 ; or a method for the synthesis of a tryptamine derivative having pharmacologically useful properties comprising said process.

36. A compound of any of the formulae XIIIa, XVI, II¹, XII¹, XIV¹, II², XII², XIV², II³, XII³, XIV³, II⁴, XII⁴, II⁵, XII⁵, XX^7 , XXI^{*} or XXI^{**} as defined in claims 21, 25, 26, 27, 28, 29, 30, 33, 34, 35, or a salt thereof.

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37. Use of a compound according to one of the claims 5, claim 6, claim 9, claim 17, claim 20, claim 23, claim 32 or claim 36 for the manufacture of a pharmaceutical.
38. Use of a compound according to one of the claims 5, claim 6, claim 9, claim 17, claim 20, claim 23, claim 32 or claim 36 for the manufacture of a pharmaceutical intended for the treatment and/or prevention of migraine conditions.
39. Use of a compound according to one of the claims 5, claim 6, claim 9, claim 17, claim 20, claim 23, claim 32 or claim 36 for the manufacture of a tryptamine derivative.
40. Use of a compound according to one of the claims 5, claim 6, claim 9, claim 17, claim 20, claim 23, claim 32 or claim 36 for the manufacture of a tryptamine derivative pharmaceutical intended for the treatment and/or prevention of migraine conditions.